Cell Metabolism
Perspective

The Stunned β Cell: A Brief History

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β cell dysfunction is sufficient to cause hyperglycemia; β cell loss is not necessary but, if severe, can be sufficient and may be accompanied by intrinsic β cell dysfunction. Clinical testing can differentiate β cell capacity from β cell glucose sensitivity but cannot ascribe either to relative changes in β cell mass versus function. However, longitudinal and intervention studies indicate that β cell glucose insensitivity (stunning) closely tracks with hyperglycemia and is, at least in part, reversible. Rescuing stunned β cells is a key therapeutic target.

The endocrine pancreas is a small, diffuse organ estimated to be made up of one million islets, each endowed with ~1000 β cells, for a total weight of ~0.9 g. Despite its size, like virtually every other organ, the endocrine pancreas has a considerable functional reserve; even simply in terms of stored hormone, pancreatic insulin content has been estimated to range from 200 to 250 units (10 days worth of supply for a healthy adult) (Rahier et al., 2008). Therefore, using its capacity and flexibility, the islets can accommodate a wide range of insulin demand. Typically, surgical removal of ~50% of the pancreas results in usually minor deterioration of glucose tolerance in man and animals. Whereas the attendant reduction in α cell number contributes to limit hyperglycemia, just about half a gram of remnant endocrine tissue can grant lifelong glucose control. Symmetrically, insulin secretion can cope with extremes of body size. For example, it has been calculated that a lean, insulin-sensitive adult may need as little as 0.5 units of insulin to dispose of an oral load of 75 g of glucose over 2 hr, whereas an obese, insulin-resistant, glucose-intolerant subject may require 45 units to perform the same task, an ~100-fold span (Ferrannini et al., 2007). Equally striking is the case of bariatric surgery: in morbidly obese, nondiabetic subjects who had lost 50 kg of weight following the operation, insulin output dropped by 60%—from a median of 65 to 25 units per day—in concomitance with normalization of insulin resistance (Camastra et al., 2005). Furthermore, an intravenous glucose bolus elicits a surge of insulin secretion within less than 1 min, a time constant of stimulus-secretion coupling only second to that of neuroendocrine systems. Thus, as a physiological unit, β cells exhibit both high-capacity—i.e., absolute rates of insulin release—and high-sensitivity properties—i.e., rapid and robust response to glucose increments.

Does β cell mass underlie β cell secretory capacity? Estimates of β cell mass in humans all rest on morphometric analyses of autopsy specimens. Subject sample size, information on clinical status, tissue preservation, dyshomogeneity of intrapancreatic islet distribution, and kind of measure (β cell relative volume versus β cell mass) confound such post mortem determinations and presumably contribute to the wide between subject variation in β cell mass found in these studies. Nevertheless, the literature is consistent in indicating that the nondiabetic obese individual has an expanded islet mass. According to the two largest and most recent studies, as compared to lean individuals with a BMI of 22–23 kg/m^2, β cell mass was increased by 20% in subjects with an average BMI of 30 kg/m^2 (Rahier et al., 2008) and β cell relative volume was increased by 50% in subjects with a BMI of 38 kg/m^2 (Butler et al., 2003), both estimates being much lower than in obese rodents. Thus, in nondiabetic subjects, estimates of β cell mass do parallel measurements of insulin secretory capacity qualitatively but fall short of a strictly proportional relationship. In particular, it is implausible that, in calorie-restricted subjects, β cells should be vanishing as insulin output decreases to the extent seen with bariatric surgery. Therefore, from a quantitative standpoint, adaptation of β cell function (i.e., activation of key enzymes and transcription factors, upregulation of genes) appears to account for the larger part of the changes in insulin secretion seen in association with changes in body size in nondiabetic individuals.

Does β cell mass determine, or even track, the dynamic properties of the β cell? This is an even more intractable question. The cellular and molecular biology of the β cell is extraordinarily complex: the β cell integrates multiple inputs—both stimulatory and inhibitory—to mount a secretory response. However, at a whole-body level, the functional behavior of β cells can be reduced to a few basic rules. Although insulin exerts actions on carbohydrate, lipid, protein, and electrolyte metabolism, the dominant physiological feedback is on glucose: what is primarily needed is to avoid hypoglycemia (life threatening) as well as hyperglycemia (in the long term, toxic to tissues) by confining plasma glucose excursions within a very narrow range (only ~3 mmol/l in normal adults). Therefore, insulin release must not only be sufficient in quantity to elicit effects in target tissues (i.e., restraining glucose output by the liver and promoting glucose uptake into muscle and fat), but also appropriate in timing: delayed secretion of normal amounts of hormone is associated with hyperglycemia (compare the blue and red insulin responses to oral glucose [OGTT] in Figure 1B: the area under the respective curves is similar, yet subjects with the red insulin response have diabetic glucose levels [Figure 1A]). In fact, to attain tighter homeostasis, insulin release must also be able to anticipate glucose rises and prevent persistent

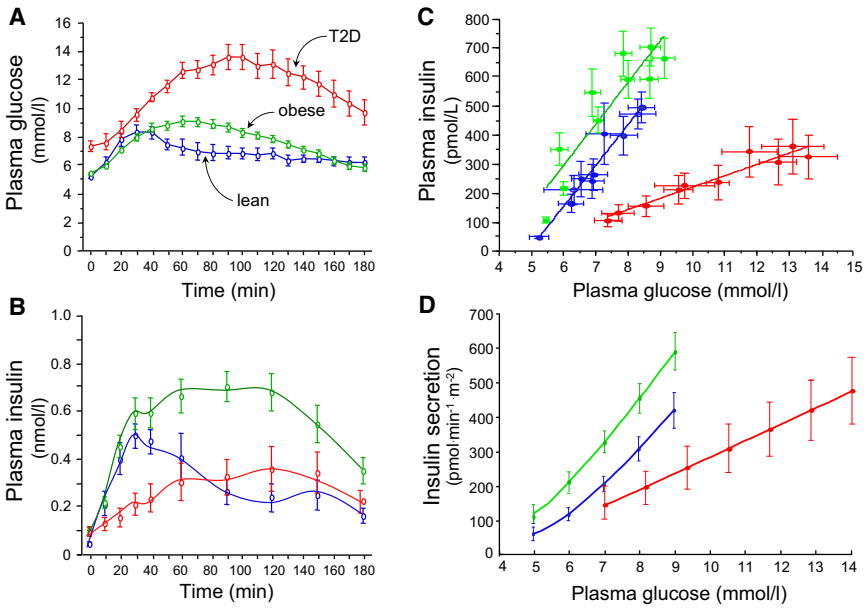

Figure 1. The Concept of β Cell Glucose Sensitivity

(A–D) Plasma glucose (A) and insulin concentrations (B) in response to an oral glucose load in lean nondiabetic subjects (blue lines), obese nondiabetic subjects (green lines) matched to the lean by glucose tolerance (i.e., fasting and 2 hr plasma glucose levels), and patients with type 2 diabetes (red lines) matched to the obese subjects by BMI. The data in (A) and (B) are plotted against each other in panel (C), with the corresponding linear fits. In (D), insulin concentrations were converted into insulin secretion rates using C-peptide deconvolution. The average slope of the lines is β cell glucose sensitivity, measured in pmol per min per square meter of body surface area per mmol/l of plasma glucose (pmol·min^{-1}·m^{-2}·mM^{-1}). Symbols plot means ± SEM (unpublished data).

glucose elevations. In pharmacodynamic terms, insulin secretion should be (1) coupled to glucose levels through a steep dose-response relationship, (2) rate sensitive by reading the rate of change in glucose levels, and (3) capable of potentiation by some form of glucose memory. These dynamic properties must be preserved across a range of absolute insulin secretion rates as demanded by obesity and insulin resistance (compare the blue and green lines in Figure 1B: the area under the green curve is approximately three times that under the blue curve, yet glucose levels are almost superimposable between the two groups [Figure 1A]). Remarkably, these basic physiological requirements are all confirmed by studies of isolated human islets, which have demonstrated dose dependency, rate sensitivity, and potentiation of glucose-induced insulin release (Henquin et al., 2006).

Nevertheless, despite the overall coherence of the in vitro with the in vivo physiology of the β cell, it is, at present, virtually impossible to tell whether any difference in β cell sensitivity (or rate sensitivity or potentiation) that is observed in vivo is due to differences in β cell mass or function. To illustrate this point, consider Figure 1C, in which the plasma insulin concentrations at the various times during the OGTT (Figure 1B) are plotted against the corresponding plasma glucose levels (Figure 1A) separately for the three groups of subjects. In the obese versus the lean subjects with normal glucose tolerance, insulin levels are higher at each given plasma glucose level, but the slope of the fitting line is similar. Thus, the set point of insulin release is shifted upwards (= enhanced capacity), but the ability to acutely increase insulin release with increasing glycemia (= glucose sensitivity) is approximately the same. This result, which could be explained by an upregulation of β cell capacity, is also theoretically compatible with the obese having more β cells, each of standard glucose capacity and sensitivity. In contrast, type 2 diabetic subjects require much higher glucose levels to achieve similar insulin concentrations to lean controls (for example, 12 versus 7 mmol/l to reach 300 pmol/l), i.e., they show impaired glucose sensitivity. Furthermore, even at high glucose levels, the majority of diabetic subjects do not reach the maximal insulin concentrations achieved by nondiabetic subjects; conversely, raising plasma glucose of the nondiabetic into the diabetic range would result in much higher insulin levels than seen in the diabetic. Incidentally, it could be argued that the pattern of results in Figure 1 is peculiar to the stimulus used, namely an oral glucose load, or that it is confounded by measures of peripheral insulin concentrations rather than true insulin secretion rates. However, Polonsky's group (Cavaghan et al., 2000) reported a similar shift in in vivo β cell glucose sensitivity in diabetic as compared to nondiabetic subjects using graded intravenous glucose infusions, which rules out confounding by gastrointestinal factors. In fact, β cell glucose sensitivity has been shown to be depressed in proportion to the degree of hyperglycemia even within the normal range of glucose tolerance (Ferrannini et al., 2005). Furthermore, when insulin secretion rates are reconstructed from C-peptide concentrations (by deconvolution analysis [Cavaghan et al., 2000; Ferrannini et al., 2005]), the pattern is the same: the slope of insulin secretion-plasma glucose dose-response relationship is flatter in diabetic than nondiabetic subjects (Figure 1D). Here again, a normal number of β cells each with impaired sensitivity would explain the data, but so would a substantially lower number of normally glucose-sensitive β cells.

In summary, even with use of such simple measurements as plasma glucose and insulin levels on a standard OGTT (Figure 1), one can retrieve and quantify meaningful differences in β cell capacity (e.g., obese versus lean) and glucose sensitivity (e.g., diabetic versus nondiabetic); neither set of differences, however, can be imputed to differences in β cell mass or function alone with certainty.

This conclusion appears to clash with the notion that β cell mass is low in diabetes, which has been revamped by recent studies reporting an average 40%–60% reduction of β cell relative volume in patients with type 2 diabetes (Butler et al., 2003). In fact, in the latter series, a halving of β cell relative volume was found also in subjects with impaired fasting glucose, a milder form of glucose

intolerance. Furthermore, a study in a small group of patients undergoing pancreatectomy (Meier et al., 2009) reported a close correlation between β cell relative area and presurgery plasma glucose response to oral glucose, a surprising finding in view of the known variability—spontaneous as well as treatment induced—of the OGTT. This kind of observation resonates with morphological and histochemical evidence documenting disarray of islet structure and amyloid infiltration in human diabetic islets. Moreover, the vast majority of gene variants that genome-wide scans have associated with type 2 diabetes are related to some aspect of β cell function or survival. Clinical testing, on the other hand, has contributed to the confusion, marred as it is by a host of methodological and interpretive difficulties. Though years of clinical research have yielded an accepted gold standard for the in vivo measurement of insulin sensitivity, namely, the euglycemic hyperinsulinemic clamp technique, β cell function is still assessed with methods employing different stimuli (glucose, arginine, glucagon, mixed meals), route (oral, intravenous), and format of administration (bolus injection, graded infusion, hyperglycemic plateau). The respective metrics have spanned from crude empirical indices (HOMA-B, insulinogenic index on the OGTT, acute insulin response on the IVGTT) to more ambitious constructs (the disposition index) and formal mathematical modeling. As a consequence, the etiologic paradigm of type 2 diabetes may have been shifting toward a "mass" problem, as the primary cause of β cell dysfunction, one that is present early in the natural history of diabetes, is possibly detectable in vivo (pending the refinement of novel imaging techniques) and therapeutically "drug-able" (using trophic factors or stem cells).

However, (1) autopsy specimens frequently are from sick patients of advanced age, whose glucose intolerance is uncertain in degree (subjects with impaired fasting glycemia might be diabetic on the OGTT) as well as duration; (2) in more recent series, β cell mass was quasi-normal at the time of clinical diagnosis of diabetes (Rahier et al., 2008) and was normal in lean patients with recent onset diabetes (Hanley et al., 2010); (3) islet amyloidosis could be the consequence, rather than the cause, of hyperglycemia; (4) when islets obtained from donors with type 2 diabetes are studied under "healthy" culture conditions, they show defective responses to glucose (Marchetti et al., 2004); (5) β cell glucose insensitivity antecedes and independently predicts the emergence of dysglycemia in young subjects with normal glucose tolerance (Walker et al., 2005), that is, at a time when β cell mass would be mostly preserved; (6) intensified insulin therapy or, indeed, any treatment resulting in marked amelioration of glycemic control is associated with partial reversal of β cell insensitivity and enhanced β cell capacity; and (7) bariatric surgery is followed by long-lasting resolution of diabetes in a high proportion of type 2 patients, in some cases with full recovery of β cell glucose sensitivity. Because, in human adults, β cell regeneration appears to occur at a very low rate, changes in β cell mass can hardly explain recovery of function; it follows that β cell mass deficit alone is unlikely to be the primary cause of most cases of diabetes, whereas β cell dysfunction theoretically could be the sole mover.

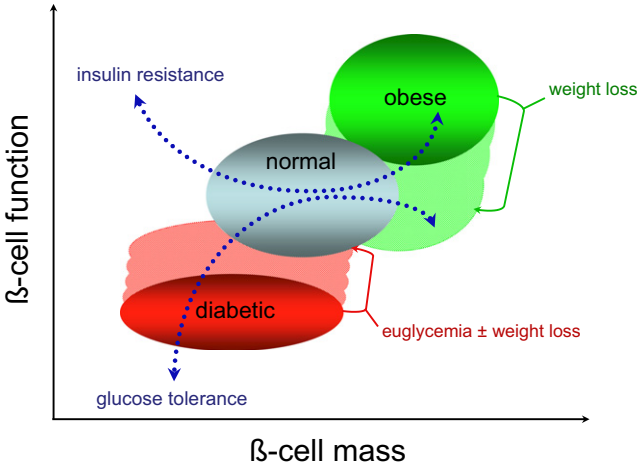

Figure 2. Schematic Plot of β Cell Function versus β Cell Mass in Normal, Nondiabetic Obese Subjects and Diabetic Subjects
The stippled areas represent the range of changes in β cell function observed with weight loss and improved glycemic control (reduced capacity and unchanged glucose sensitivity in the obese nondiabetic, increased capacity and increased glucose sensitivity in the diabetic); the corresponding changes in β cell mass are hypothetical. The dotted blue lines stand for the associated changes in glucose tolerance (marginally impaired in obesity, profoundly decreased in diabetes, reversible) and insulin resistance (present in both obesity and diabetes, reversible).

All in all, the available evidence is compatible with the following construct. β cell dysfunction is sufficient to cause hyperglycemia; reduced β cell mass is not necessary but, if severe, can be sufficient, i.e., it may or may not be associated with intrinsic β cell dysfunction. In a timescale of months or years, insulin resistance modulates β cell capacity (or set point), at least in part, by driving β cell mass expansion; the impact of obesity is partially mediated by insulin resistance. (A further level of complexity would be added if insulin resistance at the level of the β cell was negatively affecting its function or mass, a possibility that is still being explored). As a result, in obese subjects with normal glucose tolerance, β cell mass is increased, β cell capacity is upregulated, but glucose sensitivity is normal; weight loss restores capacity, possibly with some effect on β cell mass. In glucose-intolerant/diabetic subjects, mass may be reduced—particularly with long-standing hyperglycemia—and β cells are markedly dysfunctional in capacity as well as glucose sensitivity, but euglycemia and weight loss improve both modes of β cell function, presumably in the absence of major changes in β cell mass (Figure 2).

If pathogenesis can be reduced to a few interacting mechanisms, clinical diabetes is nothing like its pathogenesis, comprised as it is of multiple subphenotypes, dyshomogeneous for other factors in addition to pathophysiology. Conceivably, there are people who are born with a small pancreas, secondary to stunted growth during early pregnancy (the so-called small baby syndrome). In them, a poor endowment of β cells is the context against which acquired burden in adult life leads to glucose intolerance. In other subjects with a normal number of β cells, an intrinsic (genetic?) defect of β cell

function is the primary risk substrate for diabetes. In still another group of patients born with a normal number of normal β cells, an environmental injury slowly erodes β cell mass or paralyzes their glucose sensing but goes unnoticed and is lumped together with the other subgroups under the heading of type 2 diabetes. Finally, there are the adult patients whose β cell mass (and, perhaps, function) is compromised by a slow autoimmune attack (latent autoimmune diabetes of adulthood), who may likewise be misclassified as type 2 patients. What is of paramount importance is that, in each member of this (incomplete) list of subphenotypes, age and chronic hyperglycemia each accumulate demise of both β cell mass and function. Age conveys low-penetrance genetic influences, comorbidities, weight gain, sedentariness, vascular dysfunction, and drug toxicity. Chronic hyperglycemia is a well-known perpetrator of widespread tissue damage that hits the islet both by compromising vascular and neural supply and by directly blunting β cell response to glucose; it does so in vitro—where exposure to high glucose for a few days is sufficient to alter the subsequent secretory response to glucose stimulation—and it does so in vivo under experimental circumstances. Glucose toxicity is an undisputed fact, incompletely understood but solidly established. In support of this notion, in Rahier's autopsy series (Rahier et al., 2008), β cell mass showed a significant negative association with diabetes duration despite the great variability of the measures. An important role for the duration of hyperglycemic exposure is also borne out by in vivo data in diabetic patients, in whom β cell glucose sensitivity is reciprocally related to disease duration even after adjusting for the severity of the hyperglycemia (data not shown).

From these grounds emerges the concept that a fairly common pathophysiological element across hyperglycemic syndromes is, what can be called, the stunned β cell (by analogy with the postinfarction myocardium): a cell that is temporarily unable to appropriately sense its primary stimulus but may recover competence, at least in part. Indeed, there can be no harm in just assuming that every dysglycemic person has some stunned β cells that can be retrieved into function and that every person at risk of diabetes—for reasons of genes, birth, or environment—has β cells that can be spared from stunning. The correlation between β cell glucose sensitivity and glycemia is so tight (Figure 1) that any improvement of the former begets a decrement in the latter and vice versa. From the clinical standpoint, restoring β cell mass is a distant therapeutic aim; under the circumstances, the key target in the treatment and prevention of the epidemic of hyperglycemia is hyperglycemia itself. There are better means today than ever in the past to rescue stunned β cells. We have good evidence that revving up insulin sensitivity by insulin-sensitizing drugs will relieve pressure on an endangered β cell population, thereby inducing more durable glycemic control. Following up on the observation that GLP-1 can restore euglycemia in patients with type 2 diabetes by markedly potentiating β cell function (through cAMP-dependent pathways), incretin-based treatments (DPP-IV inhibitors and GLP-1-receptor agonists) are in clinical apprenticeship. Activating β cell glucokinase—the first committed step for glucose-induced insulin release—may be feasible in vivo if the attendant risk of hypoglycemia can be smoothed out. Several other potential therapeutic targets within the β cell are being probed pharmacologically. Glycosuric agents, which allay glucose toxicity in an insulin-independent fashion, may become usable drugs. Early, intensified insulin therapy—even just a short course of a few weeks—can grant newly diagnosed diabetic patients a lasting remission or, at least, a prolonged honeymoon phase. Early combination treatment is being explored, and oral insulin formulations may eventually exhibit an absorption pattern that is reproducible enough to be safely exploited in patients. For the time being, there appears to be sufficient rationale to propose that bringing any degree of hyperglycemia under as tight control as allowed by safety and as early as possible can awaken stunned β cells, whatever their past history and genetic program may be in the individual patient.

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